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(21) International Application Number: PCT/DK89/00112 (22) International Filing Date: 8 May 1989 (08.05.89) (30) Priority data: 8811041.6 10 May 1988 (10.05.88) GB 8822603.0 27 September 1988 (27.09.88) GB 8829368.3 16 December 1988 (16.12.88) GB (71) Applicant (for all designated States except US): LEO PHARMACEUTICAL PRODUCTS LTD. A/S (LØV-ENS KEMISKE FABRIK PRODUKTIONSAKTIE-SELSKAB) [DK/DK]; Industriparken 55, DK-2750 Ballerup (DK). (72) Inventor; and (75) Inventor/Applicant (for US only) : GODTFREDSSEN, Wagn, Ole [DK/DK]; Nørrevænget 34, DK-3500 Værløse (DK). (74) Agent: RYDAHL KRISTENSEN, P.; Leo Pharmaceutical Products, Industriparken 55, DK-2750 Ballerup (DK).		(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report.</i>
(54) Title: NEW OPHTHALMIC PREPARATION FOR TREATING GLAUCOMA (57) Abstract The present invention relates to compositions for topical application in the eye, to the use of a class of compounds, i.e. the potassium channel openers for the preparation of such ophthalmic compositions, and to a method of treating glaucoma.		

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NEW OPHTHALMIC PREPARATION FOR TREATING GLAUCOMA

The present invention relates to compositions for topical application in the eye, to the use of a class of compounds, i.e. the potassium channel openers for the preparation of such ophthalmic compositions, and to a method of treating glaucoma.

A number of members of the class of drugs called potassium channel openers have been described. In European patent application 0 076 075 a series of such compounds are disclosed. One of these has been described extensively in the literature under the name cromakalim (BRL 34915) (ref. J. Med. Chem. 29, 2194 (1986), Compound 2). German Offenlegungsschrift 2 714 713 discloses another series of compounds one of which has become known as nicorandil. In United Kingdom Patent No. 1489879 a series of potassium channel openers are described, among them N"-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine, described in the literature as pinacidil.

In the following these compounds will be referred to collectively as potassium channel openers.

The potassium channel openers have been shown to relax smooth muscles from various tissues, e.g. tracheal, vascular and ileal smooth muscles, and clinically they have been studied in the treatment of hypertension and other vascular diseases, angina and asthma.

A number of drugs have been used for topical treatment of glaucoma, a disease characterized by an increased intraocular pressure. β -Adrenergic antagonists, like timolol, lower the intraocular pressure, presumably by reducing the production of aqueous humor. However, the topical application of these drugs in the eye has been found in some cases to result in systemic effects. Therefore, this type of treatment is contraindicated in a large number of patients, e.g. asthmatics.

Cholinergic agonists, like pilocarpine, and acetyl cholinesterase inhibitors, like physostigmine, reduce the intraocular pressure by lowering the resistance to outflow of the aqueous humor, as they induce a contraction of the sphincter smooth muscle of the iris. However, these drugs have a blocking effect on accomodation, leading to blurring of far vision.

Since the cholinergic agonists owe their action to a contraction of smooth muscles, the smooth muscle relaxing potassium channel openers should be expected to increase the resistance to outflow of aqueous humor, thus increasing the intraocular pressure.

However, despite these expectations, it has now been found very surprisingly that the present compositions containing as the active ingredients a potassium channel opener can effectively and longlasting reduce the intraocular pressure in experimental animals and patients suffering from glaucoma. Furthermore, due to their bronchodilating properties the potassium channel openers, in contrast to the β -blockers, can be used without risk in patients suffering from asthma. Still further, the present preparations do not give rise to any form of irritation in the eye, have no local anaesthetic properties, and in contrast to the cholinergic agonists and the acetyl cholinesterase inhibitors they have no effect on accomodation.

Accordingly, the present invention also provides a method for the treatment of glaucoma comprising topical administration of an effective, non-toxic amount of a potassium channel opener or a pharmaceutically acceptable salt thereof to patients in need of such treatment.

Preferred active compounds are the potassium channel openers nicorandil, pinacidil and cromakalim.

Of these compounds, pinacidil in its (-)-form has shown to be the most effective for obtaining the desired result.

The effective amount of the active compound depends on the severity of the condition. However, it is believed that an amount of from 0.05 mg to 10 mg per day should be sufficient for effective treatment.

The pharmaceutical compositions contemplated by this invention include pharmaceutical compositions suited for topical application in the eye.

The compositions of the invention preferably contain
5 from 0.01% to 2% of the potassium channel opener or a pharmaceutically acceptable salt thereof.

The pharmaceutical preparation which contains the active compound may be conveniently admixed with a non-toxic pharmaceutical organic carrier, or with a pharmaceutically
10 acceptable inorganic carrier. Typical of such pharmaceutically acceptable carriers are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or vegetable oils, polyalkylene glycols, petroleum based jelly, hydroxyethyl cellulose, ethyl oleate, carboxy-
15 methyl cellulose, polyvinylpyrrolidone, and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic auxiliary substances such as emulsifying, preserving, wetting, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400
20 and 600; carbowaxes 1,000, 1,500, 4,000, 6,000 and 10,000; a polyanionic polymer, e.g. a carboxyvinyl polymer having a molecular weight of from about 4,000 to about 6 million; antibacterial components such as quaternary ammonium compounds; phenylmercuric salts known to have cold steril-
25 izing properties and which are non-injurious in use; thimerosal, methyl and propyl paraben, benzyl alcohol, phenyl ethanol; buffering ingredients such as alkali metal chloride, borate, acetate, gluconate buffers, and other conventional ingredients such as sorbitan monolaurate, tri-
30 ethanolamine, oleate, polyoxyethylene sorbitan monopalmitate, dioctyl alkali metal sulfosuccinate, monothio-glycerol, ethylenediamine tetraacetic acid and the like.

The composition may further contain other therapeutically active compounds applied in the treatment of
35 glaucoma, for instance a β -blocking agent, a cholinergic agonist or an acetylcholinesterase inhibitor.

The invention will now be further described in the following non-limiting Examples:

Example 1Eye-Drops

5 An eye preparation of the following composition per ml is prepared:

	Pinacidil monohydrate	1 mg
	Hydrochloric acid 1 N	q.s.
	for dissolution of pinacidil (approx. 7.7 micro liter)	
10	Sodium citrate	1 mg
	Benzalkonium chloride	0.1 mg
	Tetracemin disodium	0.5 mg
	Glycerol	25 mg
	Water, sterile	to make 1 ml

15 a) Pinacidil monohydrate is dissolved in hydrochloric acid 1 N by stirring or shaking.

b) Sodium citrate, benzalkonium chloride, tetracemin
20 disodium and glycerol are dissolved in sterile water.

a) is added to b) and the pH adjusted to 5.

c) Sterile water to make up to volume (weight) is added.
25

The solution is sterile filtered through a membrane filter
Cs 0.22µ.

30 Finally the preparation is filled in suitable containers for dispensing and autoclaved at 120°C.

Example 2Eye Gel

35

An eye preparation of the following composition per ml is prepared:

	Pinacidil monohydrate	1 mg
	"Carbopol 934"	10 mg
	Glycerol	25 mg
	Benzalkonium chloride	0.1 mg
5	Sodium hydroxide	q.s.
	Water, sterile	to make 1 ml

Glycerol and benzalkonium chloride are dissolved in sterile water. The pinacidil and the "Carbopol 934" is added to the
10 solution.

The suspension is neutralized by addition of aqueous solution of sodium hydroxide and the pH adjusted to pH 5.

15 Finally the preparation is filled in suitable containers for dispensing and autoclaved at 120°C.

Example 3

20 Eye-Drops

An eye preparation of the following composition per ml is prepared:

25	N-tertbutyl-N'-cyano-N"-3-pyridylguanidine (P 1060)	0.2 mg
	Hydrochloric acid 1 N	q.s.
	for dissolution of P 1060 (approx. 7.7 micro liter)	
	Sodium citrate	1 mg
30	Benzalkonium chloride	0.1 mg
	Tetracemin disodium	0.5 mg
	Glycerol	25 mg
	Water, sterile	to make 1 ml

35 a) N-tertbutyl-N'-cyano-N"-3-pyridylguanidine is dissolved in hydrochloric acid 1 N by stirring or shaking.

b) Sodium citrate, benzalkonium chloride, tetracemin

disodium and glycerol are dissolved in sterile water.

a) is added to b) and the pH adjusted to 5.

5 c) Sterile water to make up to volume (weight) is added.

The solution is sterile filtered through a membrane filter
Qs 0.22µ.

10 Finally the preparation is filled in suitable containers for
dispensing and autoclaved at 120°C.

Example 4

15 Eye Gel

An eye preparation of the following composition per ml is
prepared:

20	Cromakalim	0.2 mg
	"Carbopol 934"	10 mg
	Glycerol	25 mg
	Benzalkonium chloride	0.1 mg
	Sodium hydroxide	q.s.
25	Water, sterile	to make 1 ml

Glycerol and benzalkonium chloride are dissolved in sterile
water. The cromakalim and the "Carbopol 934" is added to
the solution.

30

The suspension is neutralized by addition of aqueous
solution of sodium hydroxide and the pH adjusted to pH 5.

35 Finally the preparation is filled in suitable containers for
dispensing and autoclaved at 120°C.

Example 5Pharmacological data. Intraocular pressure in rabbits

Male New Zealand pigmented rabbits (2.5-3.5 kg) were trained to accept handling, restraint and periodic intraocular pressure (IOP) measurements. IOP was measured in conscious animals, using a floating tip tonometer (Pneumotonograph, Alcon. Fort Worth, Texas), without prior corneal anaesthesia. The tonometer is connected with a computer (GESDAC) loaded with a program (GESDOS) allowing acquisition and screen display of 3 successive 10 seconds IOP measurements, each of them including 30 instantaneous values. The screen display of each IOP measurement enables the quality control of the readings. The mean value of 3 acceptable IOP determinations is printed on a M.T. 80 S printer.

Three rabbits with normal IOP (11.4-14.2 mmHg) at both eyes, were selected for study. They were administered 50 µl of Pinacidil 0.1% (w/v) sterile solution (Example 1) by instillation into the left and right conjunctival sac. At 8 days intervals, the same rabbits were treated in the same manner and at the same time of the day, with sterile saline and Timolol 0.5% (w/v) ophthalmic solutions (Timoptol^R, M.S.D. Chibret, France).

On each treatment day, IOP measurements were done on both eyes before instillation and 15 - 30 - 60 - 120 - 180 - 240 - 300 - 360 min. after instillation.

A single instillation of 50 µl Pinacidil 0.1% induces a rapid and sustained IOP decrease ranging from -4.2 +/- 0.8 mmHg (-32% vs. basal IOP) at +30 minutes to -1.35 +/- 0.6 mmHg (-10%) at 240 minutes. By contrast, Timolol 0.5% is followed by a limited (-2.3 +/- 1.3 mmHg; -18%) and short lasting (60 minutes) IOP decrease. With saline ophthalmic solution, IOP variations remain within the range of -1.6 +/- 1.5 to +1.25 +/- 1.2 mmHg throughout the observation period with the exception of a single time point, at 300 minutes, where an IOP decrease of -2.5 +/- 0.6 was recorded.

Variance analysis performed (i) on basal IOPs and (ii) on calculated areas under time-pressure curves (AUC) between 0-60 minutes; 0-240 and 0-360 minutes showed that basal IOPs did not differ significantly between treatment periods and that the ocular hypotensive effect of Pinacidil is highly significant ($p < 0.001$) both versus saline and Timolol ophthalmic solutions, irrespective of the considered AUC range.

10

Example 6

Corneal anaesthesia in rabbits

In a first experiment, 6 pigmented New Zealand male rabbits were randomized in 2 groups of 3. In the first group, the animals were instilled with 50 μ l Pinacidil 0.1% (w/v) sterile solution into the right conjunctival sac whereas in the second group, the rabbits received 50 μ l sterile saline ophthalmic solution in the same way. In both groups, the left eyes remained untreated. Eight days later, the same animals were administered, again in the right eye, the treatment they did not receive previously.

In a second experiment, 2 groups of 2 rabbits were instilled in both conjunctival sacs 50 μ l of either sterile saline or Timolol 0.5% (w/v) ophthalmic solutions. A third group of 2 rabbits remained untreated and served as controls.

In both experiments, the corneal reflex was tested three times in intervals of 1 minute at each time point, by means of a Cochet's esthesiometer (nylon thread: 0.12 mm diameter, 10 mm long), before instillation and 5 - 10 - 20 - 30 - 40 - 50 - 60 minutes after instillation.

The number of corneal mechanical stimuli necessary to induce a blinking reflex was not influenced by the instillation of 0.1 % Pinacidil whereas it was increased for 40 minutes after instillation of 0.5% Timolol.

Example 7

Three rabbits with normal IOP at both eyes were treated at 4 days interval by installation into the left and right conjunctival sac 50 µl of the following preparations:

5

1. Levorotary antipode of pinacidil (0.1%) ((-)-Pin)

2. Dextrorotary antipode of pinacidil (0.1%) ((+)-Pin)

10

3. Vehicle

4. Pinacidil (0.1%) ((±)-Pin)

Three other rabbits were treated in the same way at 4 days interval with the following preparations:

15

5. N-tertbutyl-N'-cyano-N"-3-pyridyl-guanidine (0.044%) (P1060)

20

6. Cromakalim (0.02%)

7. Vehicle

IOP was measured as described in Example 5 before and 30, 60, 120, 180, 240, 300, and 360 min. after installation.

25

The results are shown in Table 1.

The results show that (-)-Pin is more effective than (+)-Pin in lowering IOP in normotensive conscious rabbits. The activity of (±)-Pin is intermediary.

30

Furthermore, (±)-Pin and (-)-Pin are more active than P1060 and Cromakalim in lowering IOP in the concentrations used in this experiment.

35

Table 1:

Treatment	Concentration (%)	Number of eyes	IOP before treatment (mmHg)	Mean IOP (mmHg) at various intervals (min) after drug administration						Mean area under time-IOP curve (mmHg · min) between 0 and 360 min	
				30	60	120	180	240	300		360
Vehicle	-	12	16.8 (0.8)	17.0 (1.3)	17.4 (0.9)	17.3 (1.1)	16.6 (0.8)	16.1 (1.4)	16.2 (1.1)	16.5 (0.8)	6015.75 (223.28)
(±)-Pin	0.1	6	17.2 (0.7)	14.9 (0.9)	13.3 (1.0)	13.6 (1.2)	14.3 (1.1)	15.5 (0.8)	13.7 (0.3)	17.0 (0.5)	5246.75 (226.60)
(-)-Pin	0.1	6	16.6 (0.9)	13.2 (0.9)	12.2 (0.4)	13.5 (1.0)	13.5 (0.9)	14.1 (1.2)	12.7 (0.5)	15.5 (0.5)	4890.25 (126.27)
(+)-Pin	0.1	6	16.6 (0.7)	13.6 (2.3)	14.2 (1.2)	14.3 (0.8)	17.2 (1.4)	15.9 (1.4)	14.2 (0.7)	16.0 (1.0)	5477.75 (243.21)
P1060	0.044	6	17.0 (1.1)	19.2 (2.4)	16.1 (0.4)	14.8 (0.5)	13.7 (0.8)	16.2 (0.6)	16.5 (1.3)	15.4 (0.4)	5687.75 (145.33)
Cromekalim	0.020	6	16.6 (0.9)	19.8 (1.8)	16.8 (0.9)	12.7 (0.9)	13.8 (1.2)	14.8 (0.9)	15.8 (1.1)	15.7 (1.3)	5502.75 (170.87)

Standard deviations are shown between brackets

Standard deviations are shown between brackets

Example 8

Male HY278 albino rabbits weighing 3.0-3.5 kg were generally anaesthetised by i.v. injection of 30 mg/kg sodium pentobarbital, and the right eye was locally anaesthetised
5 by topical oxybuprocaine chloride 0.4%.

The cornea was punctured at the center with sterile double curved needle (diameter: 0.40 mm, length: 20 mm) (Hamilton), and the tip of the needle was headed to the posterior
10 chamber of the right eye through the passage left between the iris and the anterior part of the lens. Once the needle tip correctly located, 0.5 mg alpha-chymotrypsin (450 U.E.) dissolved in 0.1 ml sterile saline were gently injected into the posterior chamber.

15 The ocular condition of the rabbits was examined daily for several days after alpha-chymotrypsin injection and every rabbit presenting severe ocular inflammation was discarded.

20 The rabbits were then allowed to rest for one month and thereafter the IOP of the alpha-chymotrypsin injected eye was checked approximately once a week. Eight rabbits having a stable ocular hypertension were selected for the present study. At study onset they had been injected with alpha-
25 -chymotrypsin not less than 2 months ago (limits: 2 - 8 months) and weighed 3.5 to 5 kg.

IOP was measured as described in Example 5 before and 30, 60, 120 180, 240, 300, and 360 min. after installation at
30 one week interval into the conjunctival sac of the hypertensive eye of each animal of 50 µl of the following preparations:

35

1. Pinacidil (0.05%)
2. Pinacidil (0.1%)
- 5 3. Pinacidil (0.2%)
4. Vehicle

The effect is shown in Table 2. The table shows that the
10 elevated IOP was lowered by all concentrations of
pinacidil.

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Table 2

Treatment	Concentration (%)	Number of eyes	IOP before treatment (mmHg)	Mean IOP (mmHg) at various intervals (min) after drug administration						Area under time-IOP curve (mmHg · min) between 0 and 360 min	
				30	60	120	180	240	300		360
Vehicle	-	8	28.4 (1.5)	28.3 (2.7)	27.8 (2.6)	26.5 (2.8)	26.0 (3.0)	26.5 (2.2)	25.5 (1.5)	26.4 (1.5)	9419.1 (620.1)
Pinacidil	0.05	8	27.4 (3.9)	25.3 (4.2)	24.0 (5.2)	22.8 (2.6)	22.6 (3.8)	22.1 (2.0)	21.4 (2.3)	22.8 (1.9)	8273.4* (928.2)
Pinacidil	0.10	8	27.8 (3.3)	26.7 (3.6)	25.9 (3.2)	22.0 (3.4)	21.0 (4.2)	21.5 (3.6)	22.4 (3.1)	22.5 (2.2)	8270.7* (970.5)
Pinacidil	0.20	8	28.0 (2.1)	24.9 (3.2)	22.7 (3.6)	20.1 (3.9)	21.0 (3.6)	21.3 (3.0)	20.2 (1.4)	21.7 (2.7)	7810.5* (910.8)

- Standard deviations are shown between brackets

- * : significantly differs from vehicle value, p 0.05 (Duncan's test)

WHAT WE CLAIM IS:

1. The use of a compound selected from the group called potassium channel openers in the manufacture of a medicament
5 for the treatment of glaucoma.
2. The use according to claim 1, in which the potassium channel opener selected is pinacidil (N"-cyano-N-4-pyridyl-N'-1,2,2-trimethylpropylguanidine).
- 10 3. The use according to claim 2, in which the (-)-form of pinacidil is used.
4. The use according to claim 1, in which the potassium
15 channel opener selected is cromakalim (BRL 34915).
5. The use according to claim 1, in which the potassium channel opener selected is nicorandil.
- 20 6. An ophthalmic medicament for the use according to any one of the claims 1 to 5, which in addition to the active component contains pharmaceutically acceptable, non-toxic carriers and auxiliary agents selected from the group consisting of water and water miscible solvents,
25 emulsifying, wetting, preserving and bodying agents, a polyanionic polymer, antibacterial components, buffering agents and other conventional carriers and auxiliary agents.
- 30 7. A medicament according to claim 6 in which the active component is the (-)-form of pinacidil.
8. A medicament according to claim 7, containing pinacidil as defined in an amount of 0.01 to 2%, as such or as a
35 pharmaceutically acceptable salt.
9. A medicament according to claim 6, which in addition to

the said potassium channel opener contains a further active component applied in the treatment of glaucoma.

10. A medicament according to claim 9, in which the further
5 active component is selected from the group consisting of β -blocking agents, cholinergic agonists and acetylcholin-
esterase inhibitors.

11. The use of a compound as defined in any of the claims 1
10 to 5 for the treatment of glaucoma.

12. The use according to claim 11, of pinacidil and its
pharmaceutically acceptable salts.

15 13. The use according to claim 12 of the (-)-form of
pinacidil.

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INTERNATIONAL SEARCH REPORT

International Application No PCT/DK89/00112

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 45/06, 31/35, /40, /44

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System Classification Symbols

IPC 4

A 61 K

Documentation Searched other than Minimum Documentation
to the Extent that such Documents are Included in the Fields Searched *

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	Journal of ocular Pharmacology, vol. 1, no.4, 1985, T Yorio: "Review: Cellular Mechanisms in the Actions of Antiglaucoma drugs", pages 397-422, see especially pages 407-408.	1-10
A	International Ophthalmology Clinics, vol. 13, no 2, 1973, D Duncalf et al: "Effect of anaesthetic drugs and muscle relaxants on intra-ocular pressure", pages 21-33, see the whole document.	1-10
P,A	Chemical Abstracts vol. 110, no 7, 1989, T C Hamilton et al: "Cromakalim, nicorandil and pinacidil: novel drugs which open potassium channels in smooth muscle", abstract number 50582b & Gen. Pharmacol. 1989, 20(1), 1-9, abstract	1-10
A	DE, A1, 2 714 713 (CHUGAI SEIYAKU UK) 20 October 1977 See the whole document .../...	1-10

* Special categories of cited documents: 10

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"P" document published prior to the international filing date but later than the priority date claimed

"T" latest document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of actual completion of the international search

1989-07-27

Date of Mailing of this International Search Report

International Searching Authority

Swedish Patent Office

Signature of Authorized Officer

Niklas Forslund

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document, with indication, where appropriate, of the relevant document	Relevant to Claim No
A	GB, A, 1 489 879 (LEO PHARM. PROD. LTD) 26 October 1977 See the whole document	1-10
A	EP, A1, 0 076 075 (BEECHAM GROUP LTD) 6 April 1983 See the whole document	1-10

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 11-13, because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy
[PCT rule 39 (iv)]

2. ☒ Claim numbers 1, because ^{it is} ~~they~~ relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The active chemical compounds are not characterized by their chemical constitution but by their biological activity (potassium channel openers). Definitions of this kind lack differentiating power.

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the international Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.